CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204061Orig1s000

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	204061
Supporting document/s:	e-submission
Applicant's letter date:	5/31/2012
CDER stamp date:	5/31/2012
Product:	Quartette (LNG/EE 0.15 mg/0.02 mg, 0.15 mg/0.025 mg, 0.15 mg/0.030 mg & 0.010 mg EE tablets (DR-103)
Indication:	Contraception
Applicant:	Teva Branded Pharmaceutical Products R&D Inc.
Review Division:	Division of Reproductive & Urologic Products
Reviewer:	Krishan L. Raheja, D.V.M., Ph.D.
Supervisor/Team Leader:	Alex Jordan, Ph.D.
Division Director:	Hylton V. Joffe, M.D., M.M.Sc.
Project Manager:	Pamela Lucarelli

Date review entered in DARRTS: 10/22/12

Disclaimer

Except as specifically identified, all data and information discussed below and necessary for approval of NDA 204061 are owned by Teva Branded Pharmaceutical Products are data for which Teva Branded Pharmaceutical Products has obtained a written right of reference. Any information or data necessary for approval of NDA 204061 that Teva Branded Pharmaceutical Products does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 204061.

1 Executive Summary

1.1 Introduction: Quartette (DR-103) is an extended-regimen, oral contraceptive consisting of 84 tablets, each containing 0.15 mg of levonorgestrel, a synthetic progestogen, in combination with 0.020, 0.025 or 0.030 mg of ethinyl estradiol followed by 7 tablets containing 0.01 mg ethinyl estradiol. DR-103 was developed to systematically increase the estrogen doses at strategic points in the extended cycle when breakthrough bleeding is likely to occur, in order to reduce the incidence of overall breakthrough bleeding, while lowering the total estrogen exposure per 91-day extended cycle. With the proposed dosing schedule a systematic diminution of unscheduled bleeding and/or spotting was observed across the 4 cycles of treatment (from a median of 3.5 days per subject month in Cycle 1, to 0.8 in Cycle 4) as well as within each cycle as the estrogen dose increases.

Both Seasonique approved under sponsor's NDA 21-840 and DR-103 drug products are manufactured at the same manufacturing site, at the same commercial scale, using the same process, equipment, and in process controls.

The formulations of each DR-103 levonorgestrel/ethinyl estradiol (LNG/EE) combination tablets are identical with the exception of the varying amounts of ethinyl estradiol and the amount of lactose monohydrate.

1.2 Brief Discussion of Nonclinical Findings: Under IND 072290 dated 12/28/2011 sponsor had requested a meeting with the Division to discuss the contents and format of the proposed NDA and submitted questions for the Division. Division in lieu of a meeting provided responses in communication dated 3/29/2012. The sponsor's question for the P/T was as follows:

Sponsor' question: Teva Women's Health has not conducted a nonclinical program for Quartette, as levonorgestrel and ethinyl estradiol, alone or in combination, are well-studied and have a well-known pharmacological and toxicological profiles. Therefore,Teva Women's Health intends to reference the nonclinical pharmacology/toxicology information contained in submissions from its previously approved levonorgestrel/ethinyl estradiol oral contraceptive products NDA 21-544 [Seasonale], NDA 21-840 [Seasonique] and NDA 22-262 [LoSeasonique] to fulfill the necessary requirements for this NDA.

Does the Agency concur with this proposal?

Division response: In the pre-NDA Advice letter of March 29, 2012, the Division agreed with the Teva proposal to exclude 2.6 Nonclinical Written and Tabulated Summaries, as Teva has not conducted a nonclinical program and relying on reference to prior applications.

1.3 Recommendations

1.3.1 Approvability: P/T recommends approved of NDA 204061 for prevention of pregnancy.

1.3.2 Additional Non Clinical Recommendations: None

1.3.3 Labeling: Sponsor has submitted draft labeling

2 Drug Information

2.1 Drug: Quartette™ (received conditional approval from Office of Surveillance and Epidemiology, July 27, 2010).

CAS Registry Number (Optional)

Generic Name: levonorgestrel/ethinyl estradiol 0.15 mg/0.02 mg, 0.15 mg/0.025 mg and 0.15 mg/0.03 mg and ethinyl estradiol 0.01 mg.

Code Name: DR-103, DR-1031

Chemical Name: 18,19-Dinopregn-4-en-20yn-3-one, 13-ethyl-17-hydroxy-,(17α)-,(-)- for levonorgestrel

19-norpregna-1,3,5(10)-trien-20-yne-3,17-diol,(17α)- for ethinyl estradiol

Molecular Formula/Molecular Weight: $C_{21}H_{28}O_2$/312.5 for levonorgestrel
$C_{20}H_{24}O_2$/296.4 for ethinyl estradiol

Structure or Biochemical Description: levonorgestrel/ethinyl estradiol is a progestin/estrogen COC.

Pharmacologic Class: levonorgestrel is progestin and ethinyl estradiol is an estrogen

2.2 Relevant INDs, NDAs, BLAs and DMFs: IND 072290, NDA 21-544 (Seasonale), NDA 21-840 (Seasonique), NDA 22-262 (Loseasonique), DMF (b) (4) for levonorgestrel and DMF (b) (4) for ethinyl estradiol.

2.3 Drug Formulation: (levonorgestrel/ethinyl estradiol tablet and ethinyl estradiol tablets)

Ingredients for levonorgestrel and ethinyl estradiol tablets

Ingredients for levonorgestrel tablets consist of the following:

(b) (4) Levonorgestrel, USP
(b) (4) ethinyl estradiol, USP
anhydrous lactose, NF
hypromellose (b) (4) USP
(b) (4) cellulose, NF
magnesium stearate, NF and
(b) (4) purple for coat coloring.

Ingedients for ethinyl estradiol tablet consist of the following:

(b) (4) ethinyl estradiol, USP
anhydrous lactose, NF
polacrilin potassium, NF
(b) (4) cellulose, NF
magnesium stearate, NF and
(b) (4) yellow

2.4 Comments on Novel Excipients: Excipients used in both levonorgestrel and ethinyl estradiol tablets are not novel and are the same as the excipients used in the manufacturing of Seasonique® tablets.

2.5 Comments on Impurities/Degradants of Concern: It is stated that Ethinyl estradiol Tablets 0.01 mg meet USP monograph requirements. The drug product is tested for identification, assay, content uniformity and dissolution according to the USP or equivalent procedures.

Acceptance criteria for ethinyl estradiol degradants are stated as:

(b) (4) were set at NMT (b) (4) %;

(b) (4) ethinyl estradiol was set at NMT (b) (4) %.

Total impurities set at NMT (b) (4) %.

The acceptance criterion for individual unknown impurities is set at NMT (b) (4) %, which is less than the identification threshold of 1% descried in ICH Q3B(r2).

It is stated that there is no potential for (b) (4) to be present in the final drug substance.

2.6 Proposed Clinical Population and Dosing Regimen: Women who want to use Quartette for prevention of pregnancy.

Quartette is an extended cycle control contraceptive regimen consisting of 42 light pink tablets containing 0.15 mg levonorgestrel and 0,02 mg ethinyl estradiol, 21 pink tablets containing 0.15 mg levonorgestrel and 0.025 mg ethinyl estradiol and 21 purple tablets containing 0.15 mg levonorgestrel and 0.03 mg ethinyl estradiol, and 7 yellow tablets containing 0.01 mg ethinyl estradiol.

2.7 Regulatory Background: In December 28, 2011 correspondence, sponsor stated that Teva Women's Health has not conducted a nonclinical program for Quartette, as LNG and EE alone or in combination, are well-studied and have a well-known pharmacology/toxicology profile. Based on this information sponsor stated that they intend to reference the nonclinical pharmacology/toxicology information contained in submissions from their previously approved LNG/EE oral contraceptive products under NDAs 21-544, 21-840 and 22-262 for Seasonale, Seasonique and LoSeasonique, respectively. The Agency agreed with sponsor request not to conduct any more nonclinical toxicology studies.

3 Studies Submitted: None. All referenced to sponsor's approved NDAs 21-544, 21-840 and 22-262. The active ingredients and excipients used in these FDA approved submissions are the same as used in present NDA 204-061.

12 Appendix/Attachments: None

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISHAN L RAHEJA
10/22/2012

ALEXANDER W JORDAN
10/22/2012

45 Day NDA Meeting Checklist
Pharmacology/Toxicology

NDA Number: 204-061 **Date:** 7-9-2012
Drug Name: Quartette™ (LNG/EE 0.15mg/0.020mg, 0.15mg/0.025mg, 0.15mg/0.030mg & 0.010 mg EE tablets **Reviewer:** Krishan L. Raheja, D.V.M., Ph.D
Route of administration: Oral
Indication: Contraception
Sponsor: Teva Branded Pharmaceutical Products R&D, Inc.

Date CDER Received: 5/31/2012
Filing Date: 7/15/2012
User Fee Date:
Expected Date of Draft Review: 12/15/2012

On initial overview of the Pharm/Tox portion of the NDA application

	ITEM	YES / NO	COMMENTS
1)	On its face, is the Pharm/Tox section of the NDA organized in a manner to allow substantive review to begin?		In the pre-NDA Advice letter of 3/29/2012, the Division agreed with Teva's proposal to exclude 2.6 Nonclinical Written and Tabulated Summaries, as Teva has not conducted a nonclinical program and is relying on reference to prior applications. i.e. Seasonique® and LoSeasonique®. Moreover, the nonclinical pharmacological and toxicological profiles of LNG and EE, alone or in combination, are well-established and reported in the literature.
2)	Is the Pharm/Tox section of the NDA indexed and paginated in a manner to allow substantive review to begin?	NA	
3)	On its face, is the Pharm/Tox section of the NDA legible so that substantive review can being? Has the data been presented in an appropriate manner?	NA	
4)	Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA?	NA	

5)	If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the Sponsor clearly defined the differences and submitted reviewable supportive data?	NA	
6)	Does the route of administration used in animal studies appear to be the same as the intended human exposure? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	NA	
7)	Has the sponsor submitted a statement(s) that all the pivotal Pharm/Tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	NA	
8)	Has the sponsor submitted a statement(s) that the Pharm/Tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns?	NA	
9)	Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.57? Is information available to express human dose multiples in either mg/m^2 or comparative serum/plasma AUC levels?	Yes Yes NA	
10)	From a Pharm/Tox perspective, is this NDA fileable? If not, please state in item #11 below why it is not.	YES	
11)	Reasons for refusal to file:		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KRISHAN L RAHEJA
07/09/2012

ALEXANDER W JORDAN
07/09/2012